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50th Floor  
500 Grant Street  
Pittsburgh, PA 15219-2502  
412.454.5000  
Fax 412.281.0717  
www.pepperlaw.com**FAX INFORMATION SHEET**Date: August 6, 2004  
ID Number: 61297  
Identifier: 112911.01701

<u>Recipient's Name</u>	<u>Company</u>	<u>General Number</u>	<u>Fax Number</u>
USPTO			703-872-9306

Sender: Raymond A. Miller  
Sender's Direct Line: 412-454-5813  
Sender's Email Address: Millerra@pepperlaw.comRETURN FAX TO K. PUJOL

Total Pages Including Cover:

19

Comments: Please see attached RESPONSE TO RESTRICTION REQUIREMENT for U.S. Serial No. 09/965,967 and a Supplemental Information Disclosure Statement for U.S. Serial No. 09/965,967.

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Coversheet Page 1 of 1

PTO/SB/17 (10-03)

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**FEE TRANSMITTAL**  
**for FY 2004**

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27**TOTAL AMOUNT OF PAYMENT** (\$) 55.00**Complete if Known**

Application Number	09/966,967
Filing Date	September 28, 2001
First Named Inventor	Shi
Examiner Name	Wax
Art Unit	1653
Attorney Docket No.	112911.01701

**METHOD OF PAYMENT** (check all that apply)☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☒ Deposit Account:Deposit Account Number  
50-0436Deposit Account Name  
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The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments☒ Charge any additional fee(s) or any underpayment of fee(s)☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1001 770	2001 365	Utility filing fee	
1002 340	2002 170	Design filing fee	
1003 530	2003 265	Plant filing fee	
1004 770	2004 365	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	
<b>SUBTOTAL (1)</b> (\$)			

**2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE**

Total Claims	Extra Claims	Fee from below	Fee Paid
Independent Claims	-20** =	X	
Multiple Dependent	-3** =	X	

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description
1202 18	2202 9	Claims in excess of 20
1201 88	2201 43	Independent claims in excess of 3
1203 290	2203 146	Multiple dependent claim, if not paid
1204 66	2204 43	** Reissue independent claims over original patent
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent

**SUBTOTAL (2)** (\$)

\*\*or number previously paid, if greater; For Reissues, see above

**FEE CALCULATION** (continued)**3. ADDITIONAL FEES**

Large Entity Small Entity

Fee Code (\$)	Fee Code (\$)	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,620	1812 2,520	For filing a request for ex parte reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	55.00
1252 420	2252 210	Extension for reply within second month	
1253 950	2253 475	Extension for reply within third month	
1254 1,480	2254 740	Extension for reply within fourth month	
1255 2,010	2255 1,005	Extension for reply within fifth month	
1401 330	2401 165	Notice of Appeal	
1402 330	2402 165	Filing a brief in support of an appeal	
1403 280	2403 146	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 65	Petition to revive - unavoidable	
1453 1,330	2453 665	Petition to revive - unintentional	
1501 1,330	2501 665	Utility issue fee (or reissue)	
1502 480	2502 240	Design issue fee	
1503 640	2503 320	Plant issue fee	
1460 130	1460 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(q)	
1808 180	1808 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 770	2809 385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 770	2810 385	For each additional invention to be examined (37 CFR 1.129(b))	
1801 770	2801 385	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	

Other fee (specify)

\*Reduced by Basic Filing Fee Paid

**SUBTOTAL (3)** (\$) 55.00**SUBMITTED BY**

Name (Print/Type) Raymond A. Miller

Signature

Raymond A. Miller

Registration No. (Attorney/Agent)

42,891

(Complete if applicable)

Telephone 412.454.5000

Date

August 6, 2004

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Attorney Docket No. 112911.01701

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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AUG 06 2004

In re Application of:

Shi, et al.

Serial No. 09/965,967

: Group Art Unit: 1653

Filed: September 28, 2001

: Examiner: Wax, Robert, A.

OFFICIAL

For: COMPOSITIONS FOR PROMOTING APOPTOSIS

**RESPONSE TO RESTRICTION REQUIREMENT**

Commissioner for Patents  
Box Non-Fee Amendment  
P.O. Box 1450  
Alexandria, VA 22313-1450

This is a response to a restriction requirement mailed in the Office Action dated June 28, 2004 in the above identified application submitted herewith is a one (1) month extension, extending the period to respond to August 28, 2004. Pursuant to a telephone conference with the Examiner on Tuesday August 3, 2003, the Examiner rejoined the invention designated as Invention I (Claims 1-12 and 18-22) and Invention II (Claims 13-17). Accordingly, Applicant's restriction election is timely filed and fully responsive to the restriction requirement.

Accordingly, Applicant provisionally elects claims 1-22 with traverse.

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CLAIMS

1. (Original) A synthetic tetrapeptide that binds an Inhibitor of Apoptosis Protein (IAP) and relieves IAP-mediated inhibition of caspase activity, wherein the tetrapeptide binds a surface groove within a BIR domain of the IAP.
2. (Original) The synthetic tetrapeptide of claim 1, wherein the BIR domain is a BIR 2 domain or a BIR3 domain.
3. (Original) The synthetic tetrapeptide of claim 1, having an amino acid sequence the same as an N-terminal sequence of a cellular IAP-binding protein.
4. (Original) The synthetic tetrapeptide of claim 3, wherein the cellular IAP-binding protein is a mammalian protein or a Drosophila protein.
5. (Original) The synthetic tetrapeptide of claim 1, having a sequence X1-X2-X3-X4 (SEQ ID NO:29), wherein
  - X1 is A
  - X2 is V, T or I,
  - X3 is P or A, and
  - X4 is F, Y, I or V.
6. (Original) The synthetic tetrapeptide of claim 5, selected from the group consisting of AVPI (SEQ ID NO:1), AVAF (SEQ ID NO:2); ALAY (SEQ ID NO:3), AVPF (SEQ ID NO:4), ATPF (SEQ ID NO:5), AVPY (SEQ ID NO:6) and ATPV (SEQ ID NO:7).
7. (Original) The synthetic tetrapeptide of claim 6, which is AVPF (SEQ ID NO:4).
8. (Original) A synthetic peptide that binds IAP and relieves IAP-mediated inhibition of caspase activity, comprising the tetrapeptide of claim 1 and a C-terminal extension of one or more of up to three additional amino acid residues comprising a sequence the same as a sequence of a cellular IAP-binding protein in residues 5-7 of its N-terminus.
9. (Original) The synthetic peptide of claim 8, selected from the group consisting of:
  - (i) a pentapeptide wherein the C-terminal amino acid is Y or F;
  - (ii) a hexapeptide comprising the pentapeptide of (i) and a C-terminal amino acid which is L or I;
  - (iii) a heptapeptide comprising the hexapeptide of (ii) and a C-terminal P.

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10. (Original) The synthetic peptide of claim 9, having a sequence selected from the group consisting of AVAFYIP (SEQ ID NO:9), AIAYFLP (SEQ ID NO:10) and AVPFYLP (SEQ ID NO:11).
11. (Original) A non-peptide or partial peptide mimetic of the synthetic tetrapeptide of claim 3.
12. (Original) A non-peptide or partial peptide mimetic of the synthetic peptide of claim 8.
13. (Original) A method of stimulating apoptosis in a cell, comprising administering to the cell the synthetic tetrapeptide of claim 1, in an amount sufficient to stimulate the apoptosis in the cell.
14. (Original) The method of claim 13, wherein the cell is a cultured cell.
15. (Original) The method of claim 13, wherein the cell is disposed within a living organism.
16. (Original) The method of claim 15, wherein the organism is a mammal.
17. (Original) The method of claim 16, wherein the mammal is a human.
18. (Original) A compound that binds an Inhibitor of Apoptosis Protein (IAP) and relieves IAP-mediated inhibition of caspase activity, the compound having a formula R1-R2-R3-R4, wherein
- R1 is A or a mimetic of A;  
R2 is V, T or I, or a mimetic of V, T or I;  
R3 is P or A, or a mimetic of P or A; and  
R4 is F, Y, I or V, or a mimetic of F, Y, I or V.
19. (Original) The compound of claim 18, which is a non-peptide or partial peptide mimetic of an amino acid sequence selected from the group consisting of AVPI (SEQ ID NO:1), AVAF (SEQ ID NO:2), AIAY (SEQ ID NO:3), AVPF (SEQ ID NO:4), ATPF (SEQ ID NO:5), AVPY (SEQ ID NO:6) and ATPV (SEQ ID NO:7).
20. (Original) The compound of claim 19, which is a non-peptide or partial peptide mimetic of amino acid sequence AVPF (SEQ ID NO:4).
21. (Original) A compound that binds an Inhibitor of Apoptosis Protein (IAP) and relieves IAP-mediated inhibition of caspase activity, the compound having a formula R1-R2-R3-R4-R5-R6-R7, wherein

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R1 is A or a mimetic of A;  
R2 is V, T or I, or a mimetic of V, T or I;  
R3 is P or A, or a mimetic of P or A; and  
R4 is F, Y, I or V, or a mimetic of F, Y, I or V;  
R5 is missing, or is Y or F, or a mimetic of Y or F;  
R6 is present only if R5 is present, and is L or I, or a mimetic of L or I;

and

R7 is present only if R5 and R6 are present, and is P or a mimetic of P.

22. (Original) The compound of claim 21, comprising a partial peptide or non-peptide mimetic of an amino acid sequence selected from the group consisting of AVAFYIP (SEQ ID NO:9), AIAYFLP (SEQ ID NO:10) and AVPFYLP (SEQ ID NO:11).

23. (Withdrawn) A method of making a drug suitable for treating cell proliferative disease in a mammal by promoting apoptosis in proliferatively diseased cells, the method comprising:

a) constructing a compound that binds a mammalian IAP and relieves IAP-mediated inhibition of caspase activity, wherein the compound binds a surface groove within a BIR3 domain of the IAP; and

b) determining whether the compound promotes apoptosis in a proliferatively diseased cell, an affirmative determination indicating that the drug is suitable for treating the cell proliferative disease.

24. (Withdrawn) The method of claim 23, wherein the cell proliferative disease is cancer.

25. (Withdrawn) The method of claim 23, wherein the compound constructed is a partial peptide or non-peptide mimetic of a tetrapeptide having an amino acid sequence the same as an N-terminal sequence of a cellular IAP-binding protein.

26. (Withdrawn) A method of screening for a compound that binds an IAP at a surface groove within a BIR domain, the method comprising:

a) providing a synthetic tetrapeptide that binds a selected IAP and relieves IAP-mediated inhibition of caspase activity, wherein the tetrapeptide binds a surface groove within a BIR domain of the IAP;

b) combining the tetrapeptide and the IAP in the presence of a test compound under conditions wherein, in the absence of the test compound, a pre-determined quantity of the tetrapeptide would bind the IAP; and

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c) determining if the quantity of the tetrapeptide bound to the IAP is decreased in the presence of the test compound, the decrease being indicative that the test compound binds the IAP and relieves IAP-mediated inhibition of caspase activity.

27. (Withdrawn) The method of claim 26, which further comprises the step of determining if the test compound modulates IAP-mediated inhibition of caspase activity.

28. (Withdrawn) The method of claim 27, wherein the modulating comprises relieving IAP-mediated inhibition of caspase activity.

29. (Withdrawn) The method of claim 27, wherein the modulating comprises promoting IAP-mediated inhibition of caspase activity.

30. (Withdrawn) The method of claim 26, which further comprises the step of determining if the test compound modulates cellular apoptosis.

31. (Withdrawn) The method of claim 30, wherein the modulating comprises promoting apoptosis.

32. (Withdrawn) The method of claim 30, wherein the modulating comprises inhibiting apoptosis.

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REMARKS

In the Office action dated June 28, 2004, the Examiner required restriction of the claims as follows (i) Invention I, claims 1-12 and 18-22, drawn to synthetic tetrapeptide or mimetic; (ii) Invention II, claims 13-17, drawn to a method of stimulating apoptosis, (iii) Invention III, claims 23-25 drawn to a method of making a drug suitable for treating cell proliferative disease in a mammal by promoting apoptosis in proliferatively diseased cells which includes an assay for apoptosis-inducing activity; and (iv) Invention IV, claims 26-32, drawn to a method of screening for a compound that binds IAP. In the telephone conference of August 3, 2004 the Examiner agreed that the restriction between Groups I and II was improper, however, he maintained the restriction requirement between the rejoined Group I and II and Invention Groups III and IV.

Applicant respectfully traverses the remaining restriction requirement and respectfully requests reconsideration. In order to be fully responsive, Applicant has provisionally elected, with traverse, the invention defined by claims 1-22. By this election, Applicant does not admit, nor does Applicant waive the right to argue against at a later date, the Examiner's statement that the groups of inventions are patentably distinct. Applicant expressly reserves the right to present the claims of Invention Groups III or IV, or other claims, in one or more divisional, continuation, or continuation-in-part applications at a later date.

Applicant does not believe that the Examiner would be seriously burdened by a search for each of Groups I-IV since the subject matter of the search for the claims of Group I and Group II would greatly overlap, if not be identical, to the search for the claims of Group III and Group IV. A search for Groups I and II of the tetrapeptide itself would necessarily include the methods of Group III and Group IV.

Applicant appreciates the Examiner rejoining Invention Group I and Invention Group II. In view of the above election and remarks, Applicant believes that the restriction requirement is inappropriate. Favorable resolution is respectfully requested.

This response has been timely filed. Accordingly, no additional fee is required. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

ATTORNEY DOCKET NO. 112911.01701

PATENT

Should the Examiner have any questions or comments, or need any additional information from Applicant's attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,



By: \_\_\_\_\_  
Raymond A. Miller  
Reg. No. 42,891

Dated: August 6, 2004

PEPPER HAMILTON LLP  
500 Grant Street  
One Mellon Bank Center, 50<sup>th</sup> Floor  
Pittsburgh, PA 15219  
(412) 454-5813  
(412) 281-0717 - facsimile